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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/574,545	04/05/2006	Enrico Anthony Antonini	1679 WO/US	4059

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EXAMINER	
CHANDRAKUMAR, NIZAL S	
ART UNIT	PAPER NUMBER
1625	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/574,545	ANTONINI, ENRICO ANTHONY	
	Examiner	Art Unit	
	Nizal S. Chandrakumar	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-25 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-25 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This application filed 04/05/2006 is a 371 of PCT/US04/35386 10/22/2004 which claims benefit of 60/515,274 10/29/2003.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2,3,9,19,20,22-25rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites 'highly pure' without distinctly stating what high purity means. The specification does not define 'high purity'.

The terms 'about' in claims 2,3,9,19,20,22-24 render the metes and bounds of the claims vague and unclear.

The terms "substantially' in claim 25 render the metes and bounds of the claims vague and unclear.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for one set of condition for the purification of fentanyl, does not reasonably provide enablement for the wide variety of hplc conditions claimed. The specification does not enable any person skilled in

the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The determination that "undue experimentation" would have been needed to make and use the claimed invention is not a single, simple factual determination. There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors include 1) the breadth of the claims, 2) the nature of the invention, 3) the state of the prior art, 4) the level of one of ordinary skill, 5) the level of predictability in the art, 6) the amount of direction provided by the inventor, 7) the existence of working examples, and 8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

All of the factors have been considered with regard to the claim, with the most relevant factors discussed below:

The claims are drawn to generically 'impure preparation' of fentanyl. Further the generic methods are claimed to be available for industrial processes, meaning large scale purification for all 'impure preparation'. The list of stationary phase includes, silicon based supports, neutral supports, basic supports, acidic supports rendering the breadth of the claims wide.

Though rphplc has long been known for the purification of a wide variety of compounds and is a routinely used method for purification, any applicable method of large scale purification, in general require, method development, scale-up and validation (see rejection under 35 U.S.C. 103). These in turn depend on the impurity present in the sample to be purified, the amount of impurity, the size of the sample, the solid stationary support, the eluent, rate of elution etc. There are many factors to be considered to achieve a reproducible method specially for industrial applications. For example, relative to the desired sample (fentanyl), different impurities (depending on the source of impure fentanyl) will have different retention times, resulting in different the peak separation. This will necessitate method

development with regards to particle size, solid support, solvent (eluent) combinations, buffers, rate of elution etc. For example, for one such variable, namely Loading Ratio (sample size vs. column size), the specification on page 10, line 1 of Example 2, provides a cautionary note. With one Si-C8 ligand column specification, the results presented in Tables I and II show variability with regards to yield (see page 9 Table I , last column) that was not predicted. As such optimization and validation of developed methods would require undue experimentation for all the generically claimed 'impure preparations' and for all the plethora of solid supports and eluents claimed. While certain amount of experimentation would be required for any endeavor, in this particular case of process for industrial application, too many parameters are involved that need undue experimentation for being useful. The existence of many unpredictabilities establishes that the contemporary knowledge in the art of high performance liquid chromatography, would prevent one of ordinary skill in the art from accepting the disclosed process with one set of variables with regard to stationary support, eluent (ACN-water) etc, such as the one present in the specification on its face as universally applicable for all the conceivable set of variable situations claimed.

There is a substantial gap between what is taught in the specification and what is being claimed. Because of the limited working example and, academic nature of discussions about rphplc in the specification, one of ordinary skill in the art would be faced with undue amount of experimentation to use the invention to the full scope of the claims.

Genentech Inc. v. Novo Nordisk A/S (CA FC) 42 USPQ2d 1001, states, "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Limiting the claims to silica with C8 ligands for the solid stationary phase and defining the source of the impure fentanyl preparation would overcome this rejection.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

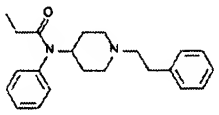
The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

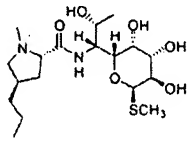
Claims 1-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hofstadter (1982, US 4,317,903).

Instant claims

The instant claims drawn to an industrial process for the purification of fentanyl using reverse phase high performance liquid chromatography. The structure of fentanyl is shown below.



Fentanyl



Lincomycin

Prior Art

Hofstetter teaches an industrial process for the purification of Lincomycin using reverse phase high performance liquid chromatography. Lincomycin (structure shown above), like fentanyl, morphine, hydrocodone and naltrexone is a tertiary amine and is anticipated to have similar chromatographic

properties. Hofstetter teaches chromatographic purification using silanized silica stationary support, including all the details such as loading ratio; solvent etc.

The difference

Hofstetter does not teach the purification of fentanyl by reverse phase high performance liquid chromatography. Hofstetter does not teach all the broadly stated limitations of the instant claims

However, one skilled in the art of process research developing alternate methods of purification of fentanyl would be motivated to modify the process of Hofstetter for the purification of fentanyl because Hofstetter teaches the conditions necessary of purification of a similar compound with similar chromatographic properties. Substituting fentanyl for lincomycin in the process of Hofstetter would require routine optimization of conditions, but this would be within the capabilities of one skilled in the art. As such one of ordinary skill in the art of organic process research, by routine optimization of existing processes of Hofstetter, by altering by mere substitution of one element for another known in the art, would arrive at the limitations of instant claims.

Prior art not relied upon:

Reversed-phase high-performance ***liquid chromatographic*** separation of fentanyl homologs and analogs. An optimized isocratic chromatographic system utilizing absorbance rationing. Lurie, Ira S.; Allen, Andrew C.; Issaq, Haleem J. Journal of Liquid Chromatography (**1984**), 7(3), 463-73.

Reversed-phase high-performance ***liquid chromatographic separation*** of fentanyl homologs and analogs. II. Variables affecting hydrophobic group contribution Lurie, I. S.; Allen, A. C. Journal of Chromatography (**1984**), 292(2), 283-94

Simultaneous determination of fentanyl and midazolam using high-performance ***liquid chromatography*** with ultraviolet detection. Portier, E. J. G.; de Blok, K.; Butter, J. J.; van Boxtel, C. J. Journal of Chromatography, B: Biomedical Sciences and Applications (**1999**), 723(1 + 2), 313-318.

Methods for the large scale synthesis of psoralen furna-side monoadducts and diadduccts. Hearst et. al. Proceedings of the National Academy of Sciences, USA. 1992, 89, 4514-4518.

Preparative separation of steroids by reverse phase HPLC. Sergio et al. EP 1398320 A1

No claim is allowed.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-25 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims of copending Application No. 10/501353, 11/576059,11/916036. Although the conflicting claims are not identical, they are not patentably distinct from each other because the subject matter of all the claims relates to processes of reverse phase high performance liquid chromatographic purification methods for samples that are anticipated to have similar chromatographic behavior. As such routine method of process described in application would provide methods for the purification of other similar compounds.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nizal S. Chandrakumar whose telephone number is 571 272 6202. The examiner can normally be reached on 8.30 AM - 4.30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on 571 0272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

nc

Nizal S. Chandrakumar

D. MARGARET SEAMAN
PRIMARY EXAMINER